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DOI: https://doi.org/10.1111/apt.15608

Letter: *Helicobacter pylori* in proton pump inhibitor-associated biliary disease

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EDITORS,

Min et al,[1] in their cohort study, proposed the role of proton pump inhibitors (PPI) as a risk factor of cholangitis, especially during the period of their use. This observational result could include unrecog- nized confounders, one of which to consider being the overlap be- tween *Helicobacter pylori* infection (*Hp*-I) and the conditions treated using a PPI; dyspepsia, peptic ulcer disease and, at least in some pop- ulations, gastro-oesophageal reflux disease—Barrett's oesophagus— oesophageal cancer sequence are associated with *Hp*-I and represent the most frequent indications for PPI prescription.[2] Moreover *Hp-I* is involved in PPI-related disorders discussed by the authors.[1-3]

The impact of *Hp*-I with biliary tree diseases has been described. Bile stasis has primarily been connected with hepatobiliary *Hp* con- tamination, thus leading to a threefold risk of chronic lithiasis and cholecystitis, triggered by a perpetual inflammation of the gallblad- der.[4,5] In this respect, our data indicated *Hp* presence in gallbladder tissue in 19.33% of patients who were submitted to cholecystec- tomy due to lithiasis,[6] while chronic biliary *Hp*-I has been identified in 75% of patients with gallbladder cancer.[7]

The proposed routes of contamination, although unproved, in- clude ascending migration through the sphincter of Oddi and hae- matogenous spread to the liver and then excretion into bile. In this respect, the potential influx of activated monocytes infected with *Hp* (due to defective autophagy) from the circulation into the gall- bladder might relate to gallbladder-related pathologies ("Trojan horse" pathway); biliary excretion of *Hp* invaded macrophages might trigger proinflammatory cytokine release, oxidative stress and inflammation, thus promoting gallstone formation and its

complications (cholecystitis/cholangitis/pancreatitis). Additionally, biliary *Hp*-I could provoke an imbalance of apoptotic cellular pro- cesses and contribute to biliary carcinogenesis. In vitro data support this, indicating that *Hp* promotes cell proliferation and suppresses apoptosis of human intrahepatic biliary epithelial cells by increasing reactive oxygen species release.[8] Finally, the authors suggested as a possible pathogenetic mechanism of PPI-related cholangitis, the imbalance between the normal small intestine microbiota and the bacterial overgrowth due to gastric acid suppression.[1] Nevertheless, *Hp*-I seems to cause more significant alterations in gut microbiota than PPI use, thus contributing to biofilm formation.[9]

Hp-I has also been associated with a plethora of extragastric conditions, such as cardiovascular and neurodegenerative diseases, glaucoma, gastrointestinal tract oncogenesis, non-alcoholic fatty liver disease and hepatic encephalopathy.[10] Therefore, it seems rea- sonable to consider adjusting for the presence of *Hp*-I as a potential cofounder in PPI-related disorders, as it is perhaps potentially rele- vant to a wide range of conditions necessitating their use.

ACKNOWLEDGEMENT

Declaration of personal interests: None. **FUNDING INFORMATION**

None.

LINKED CONTENT

This article is linked to Min et al paper. To view this article, visit https://doi.org/10.1111/apt.15466.

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